09-08-03

AF/1637

Docket No: AM100012OX1
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of:	MARK et al.		
Application No.:	09/425,501	Group Art No.:	1637
Filed:	October 22, 1999	Examiner:	CHUNDURU
For:	PABLO, A POLYPEPTIDE THAT INTERACTS WITH BCL-XL AND USES RELATED THERETO		
Confirmation No.:	9642		
Customer Number:	25291		

Mail Stop Appeal Brief-Patents
Commissioner for Patents
PO Box 1450
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TRANSMITTAL OF APPEAL BRIEF (PATENT APPLICATION - 37 CFR 1.192)

1. Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal filed on May 5, 2003.

2. FEE FOR FILING APPEAL BRIEF
Pursuant to 37 CFR 1.17(c), the fee for filing the Appeal Brief is $320.00.

3. EXTENSION OF TERM
The proceedings herein are for a patent application and the provisions of 37 CFR 1.136 apply.

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EV 238504860 US addressed to the Commissioner for Patents, Mail Stop Appeal Brief-Patents, PO Box 1450, Alexandria, VA 22313-1450.

9/5/03
Date

Elizabeth Ruzich
Elizabeth Ruzich

(complete (a) or (b) as applicable)

(a) ☒ Applicant petitions for an extension of time for the total number of months checked below.

☐	One Month.	Fee in the amount of	$ 110.00
☒	Two Months.	Fee in the amount of	$ 410.00
☐	Three Months.	Fee in the amount of	$ 930.00
☐	Four Months.	Fee in the amount of	$ 1,450.00
☐	Five Months.	Fee in the amount of	$ 1,970.00

If an additional extension of time is required, please consider this a petition therefor.

(Check and complete the next item, if applicable)

☐ An extension for months has already been secured and the fee paid therefor of $0.00 is deducted from the total fee due for the total months of extension now requested.

☒ Extension fee due with this request: $410.00

(b) ☐ Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

4. TOTAL FEE DUE

THE TOTAL FEE DUE IS:	
Appeal brief fee	$320.00
Extension fee (if any)	410.00
TOTAL FEE DUE:	$730.00

5. FEE PAYMENT

☒ Charge fee to Deposit Account No. 07-1060. This is a request to charge for any additional extension and/or fee required or credit for any excess fee paid. A duplicate of this petition is attached.

Gavin Bogle

Limited Recognition Under 37 C.F.R. §10.9(b)

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (617) 665-8079
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I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Wyeth.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellants, Appellants' legal representative, or the assignees, which will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 43, 44 and 49-65 are pending in the application. The pending claims are all on appeal and are set forth in Appendix A of this Brief.

IV. STATUS OF THE AMENDMENTS

A Final Office Action was mailed February 5, 2003, rejecting all pending claims of the instant application. A Notice of Appeal was filed on May 5, 2003, and received by the U.S. Patent Office on May 5, 2003.

V. SUMMARY OF THE INVENTION

The present invention is based, at least in part, on the discovery of protein and polypeptides derived therefrom, which interact with Bcl-xL. These proteins are useful as modulating agents in regulating a variety of cellular processes.

Applicants' invention pertains to nucleic acid molecules comprising nucleotide sequences encoding an isolated human Bcl-xL binding protein comprising the amino acid sequence as set forth in SEQ ID NO: 2 (see, e.g., page 29, line 29 through page 30, line 6). The invention also pertains to the isolated nucleic acid sequence as set forth in SEQ ID NO: 1 (see, e.g., page 19, line 1 through page 19, line 21). The Bcl-xL binding protein modulates apoptosis (see, e.g., the specification at page 73, lines 9-11). The invention further pertains to variants of the isolated human Bcl-xL binding protein which have a high degree of homology to SEQ ID NO: 2 and to nucleic acids which encode fragments of the Bcl-xL binding protein which retain its binding activity (see, e.g., page 99, lines 14-16). The invention further pertains to genetically engineered host cells transfected, transformed or infected with the vector. These embodiments find support in the specification, e.g., at page 47, lines 10-15. The invention further

pertains to neuronal cell lines stably expressing a Pablo polypeptide or an isolated Bcl-xL binding protein as set forth in SEQ ID NO: 2. These embodiments find support in the specification, e.g., at page 57, line 29 through page 58, line 8. The invention further pertains to isolated nucleic acid molecules comprising a nucleotide sequence encoding an isolated mammalian fusion protein having an amino acid sequence of SEQ ID NO: 2, wherein the protein modulates apoptosis (see, e.g., page 48, lines 14-28).

VI. STATEMENT OF ISSUES PRESENTED FOR REVIEW

Applicants present the following issues for review:

I. Whether the subject matter of claims 43, 44, 49, 50, 51, 54, 55, 56, 57, 58, 59, 60, 61, and 65 are patentable in light of Nagase et al.

II. Whether the fragments of claims 52, 53, 62, 63, and 64 are supported by adequate written description, and are patentable in light of Nagase et al.

VII. GROUPING OF CLAIMS

Applicants respectfully submit that the pending claims do not stand or fall together. Applicants have grouped the claims into two separate sections. The discussion of why the claims do not stand or fall together can be found in the Arguments section under the heading: Grouping of Claims.

VIII. ARGUMENTS

Claim Rejections Under 35 U.S.C. §102(b) for Full-Length Sequence

Claims 43, 44, 49, 51, 54, 55, 56, 57, 59, 60, 61, and 65 stand rejected under 35 U.S.C. §102(b) as anticipated by Nagase et al. (DNA Res., *Prediction of the Coding Sequences of Unidentified Human Genes*, 3: 321-329, 1996; courtesy copy included in Appendix B). Applicants respectfully submit that Nagase does not anticipate the instant invention because Nagase does not provide an enabling disclosure because Nagase discloses no use whatsoever for the bare sequences disclosed. The standard for enablement is set forth in 35 U.S.C. §112, first paragraph:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same. [Emphasis added.]

To anticipate an invention a reference must provide an enabling disclosure, *In re Hoeksema*, 399 F.2d 269, 273 (CCPA 1968). The Examiner states (Appendix C, paper no. 24, page 3) that the "enablement issue is not relevant in the present context." Applicants respectfully disagree. It is black letter law that a reference must enable the claimed invention to be considered anticipatory (*Hoeksema* at 1499-1500). In *Hoeksema* a reference was found to not anticipate, because the reference only disclosed the primary structure of the chemical. The prior art disclosure was considered merely a mental concept and a formula on paper, and thus non-enabling. See also *Seymour v. Osborne*, 78 U.S. (11 Wall.) 516, 555 (1870):

> Patented inventions cannot be superseded by the mere introduction of a foreign publication of the kind, though of prior date, unless the description and drawings contain and exhibit a substantial representation of the patented improvement, in such full, clear, and exact terms as to enable any person skilled in the art or science to which it appertains, to make, construct, and practice the invention to the same practical extent as they would be enabled to do if the information was derived from a prior patent. [Emphasis added.]

The primary structure of a protein is defined in the art as "the sequence of amino acids and location of disulfide bridges, if there are any" (Stryer, L., Biochemistry, 32 (5th ed. 1981); a courtesy copy of the relevant page is provided in Appendix B). Nagase only discloses the primary structure of the DNA and discloses no use at all for that DNA and so the situation is therefore analogous to *Hoeksema*. It follows that Nagase does not anticipate the rejected claims. Furthermore, because Nagase merely provided a primary structure without an indication of a use for the invention, Nagase does not provide an enabling disclosure of the instant invention and therefore does not anticipate the present invention.

Nagase does not suggest that the peptide encoded by the disclosed DNA will bind to Bcl-xL or that the peptide will modulate apoptosis. Nagase does not disclose how to use the invention at all. Nagase does not provide an enabling disclosure and therefore does not put the public in possession of the invention. As stated by the court in *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962):

> [The reference must] exhibit a substantial representation of the patented improvement, in such full, clear, and exact terms as to enable any person skilled in the art or science to which it appertains, to make, construct, and practice the invention to the same practical extent as they would be enabled to do if the information was derived from a prior patent. Mere vague and general representations will not support such a defense, as the knowledge supposed to be derived from the publication must be sufficient to enable those skilled in the art or science to understand the nature and operation of the invention and to carry it into practical use. Whatever may be the particular circumstances under which the publication takes place, the account publication takes place, the [sic] to support such a defense, must be an account of a complete and operative invention capable of being put into practical operation. [Emphasis added.]

The Examiner views Nagase as an anticipating reference because he claims Nagase is operable (Appendix C, paper no. 24, page 2). In the Examiner's view, operability is contingent upon the ability to synthesize the invention given a combination of the reference and the knowledge in the art. The Examiner cites the MPEP at 2121.02 for support, which states that: "One of ordinary skill in the art must be able to make or synthesize [the invention]." Applicants are not refuting the ability of one skilled in the art to synthesize the sequence given the teaching in Nagase. Rather, Applicants point out that the ability to make or synthesize the invention does not displace the requirement that a reference must be enabling for the invention and that enablement requires a disclosure of how to make *and use* the invention.

The cases cited by the Examiner are not on point and merely show that in the chemical arts the utility of an invention is often well established, while the synthesis of compounds is difficult. In the biotechnology arts, the synthesis is often not problematic but clearly the enablement and utility requirements of 35 U.S.C. §112, first paragraph may be. The process for making DNA is not in dispute. The issue is whether the primary chemical structure or "name" of the particular DNA molecule is sufficient to contain an enabling disclosure, which it is not. The mere mention of the primary structure of the DNA molecule, alone, is not enabling.

Claim Rejections Under 35 U.S.C. §102(b) for Fragments

Claims 52, 53, 62, 63, and 64 stand rejected under 35 U.S.C. §102(b) as anticipated by Nagase. Applicants respectfully disagree. Even if Nagase is found to anticipate the full length sequence, and applicants do not concede that it does, the fragments disclosed are patentable over the full length sequence because as stated in *Messerschmidt* v. *U.S.*, 29 Fed. Cl. 1, 21 (Fed Cl. 1993), "a prior art reference to a genus anticipates no species which discloses a novel invention." Nagase provides no disclosure of the structure of any useful fragments. The fragments are patentably distinct from the full-length sequence because they contain the specific binding sites that modulate apoptosis while Nagase makes no suggestion of any binding sites or the sequence's function as a modulator of apoptosis. The patentability of a species over a genus is further illustrated in *Minnesota Mining v. Johnson & Johnson*, 976 F.2d 1559, 1572 (Fed. Cir. 1992):

> The Master found no anticipation because the Straube patent does not include any mesh size or thickness parameter for the knit fiberglass fabric substrate mentioned in the Garwood claim. The Master found that the ranges 3M extrapolated from Straube are "so broad as to be meaningless to one skilled in the art. The Straube patent provides no guidance as to how to construct a fiberglass cast with the beneficial properties achieved by the Garwood invention; strength, porosity, lightness, and ability to cure quickly." The Master recognized that although Garwood's specific claims are subsumed in Straube's generalized disclosure of knit fiberglass as a substrate, this is not literal identity. [Emphasis added.]

Nagase has disclosed a segment of DNA but has not pointed the way to the claimed fragments, which encode the binding domain for Bcl-xL. Nagase, therefore, does not put one skilled in the art in possession of the useful and specific fragments claimed.

Claim Rejections Under 35 U.S.C. §112 First Paragraph

While it is unclear which claims the Examiner is rejecting, Applicants believe claims 50, 52-53, 55, 58 and 62-65 stand rejected under 35 U.S.C. §112 first paragraph.

a. Hybridization

Claims 50, 55 and 58 are herein treated as rejected with respect to their hybridization language.

The Examiner rejects the hybridization claims (Appendix C, paper no. 21, page 5) as lacking "description of fragments or complementary nucleic acid sequence [sic] that

hybridize to SEQ ID NO: 1." He further asserts (Appendix C, paper no. 24, page 4) that, "[b]y permutation and combination, there would be over several thousand possible fragments, if not millions." In response, Applicants refer to the PTO Synopsis of Application of Written Description Guidelines[1]. Therein, the PTO states at page 36 that an invention is adequately described when: "the essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO: 1 under highly stringent conditions and encodes a protein with a specific function." Their example of "highly stringent hybridization conditions" at page 38 is "6XSSC and 65 degrees Celsius."

Claims 50, 55, and 58 meet the requirements of the Written Description Guidelines. Claim 50 states that the "nucleotide sequence hydridizes to the complement of a nucleotide sequence set forth in SEQ ID NO: 1 which encodes a Bcl-xL binding protein" under the highly stringent conditions of "6X SSC at 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C." As stated in *Enzo* at 1327 "claims to nucleic acids based on their hybridization properties...may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." Therefore the Applicants respectfully request the reversal of this rejection.

b. Fragments

Claims 52-53, and 62-65 are herein treated as rejected with respect to claiming fragments encoding a Bcl-xL binding domain.

The Examiner objects to the fragment claims (Appendix C, paper no. 21, page 4) because "[t]he recitation of amino acids 419-559 or 429-559 in [sic] Bcl-xL binding domain in claim 2 do not specify the exact site for binding. Further no information is given regarding a methodology to determine such common elements or attributes. Further, there is no description of fragments." The Examiner has provided no evidence to support these assertions. As stated in the application on page 9, "[p]referred Bcl-xL binding domains are approximately 120-150 amino acid residues in length." The Examiner also states at page 9 that the "Pablo Bcl-xL binding domain comprises from

[1] The Guidelines were cited with approval by the Court of Appeals for the Federal Circuit in *Enzo*

about amino acid 419 to about amino acid 559 or about amino acid 429 to about amino acid 559 of SEQ. ID NO:2." The Examiner also states (Appendix C, paper no. 24, page 4) that the "[s]pecification cannot be read into the claims." The function of the specification in this instance, however, is to support the claims. It is not an issue of the specification being the source of limitations that are being read into the claims because the claims specify the binding domain as 419-559 or 429-559, where the binding protein fragment modulates apoptosis. Applicants respectfully request the reversal of this rejection.

Claim 65 is rejected through its dependency to the independent claim 52. Examiner misstates the dependence, however, as claim 65 is independent. Reversal of this rejection is requested.

Policy

Applicants believe that the Examiner has placed too much emphasis on case law related to chemical inventions. Applicants respectfully point out that as a biotechnology case, this application presents a good opportunity for the USPTO to depart from the narrow framework provided by chemical case law.

It is well known that modern biotechnology law has evolved from a heritage of chemical case law. E.g., in a case involving DNA and cDNA from human and bovine heparin-binding growth factors (*In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)), the basis for a prima facie case of obviousness was considered using an example of *chemists* creating compounds with similar properties with respect to homology, analogs, and isomers. In the biotechnology case *Enzo* at 1329, steroids were described only in terms of their ability to lessen inflammation as an example of insufficient written description.

The law, however, has evolved differently for the chemical arts and for the biotechnology arts in some situations. The cases involving written description and utility provide examples of this departure. E.g., *Enzo* at 1326 states that a biological deposit may be necessary to satisfy written description and enablement requirement for claims to microorganisms because it is possible for the description of how to make the invention to

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Biochem, Inc. v. *Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002)

be inadequate to make the claimed invention. Indeed a deposit may be sufficient to satisfy these requirements (*Enzo*, 1326). Deposits are not relevant in chemical cases because the formula of the compound and a description of how to make it are generally sufficient.

In re Schoenwald, 964 F.2d 1122 (Fed. Cir. 1992) is a chemical case argued on 35 U.S.C. 101 grounds which found that a utility was not required to be disclosed for prior art to be anticipating. The reasoning in *Schoenwald* should not be applied to the instant application as the applicant in that case did not dispute that the prior art was enabled (*Schoenwald*, 1122).

The court in *Schoenwald* found that the use of a chemical compound is inherent to its structure and therefore the discovery of a new use "can not impart patentability to claims to the known composition" (*Schoenwald*, 1124). This rational, however, should not be applied to the biotechnology arts because isolated DNA does not have any intrinsic function. One cannot know the function of a sequence by looking at the DNA, as one can with chemicals. This is the reason the utility and written description guidelines were promulgated. The utility of isolated DNA is that it encodes information that cannot be deduced from the sequence alone but which, when combined with other knowledge, can define a patentable invention. Unlike a small organic molecule, which has an intrinsic and perhaps undiscovered use, the sequence of an isolated molecule of DNA, without more, has no use at all.

Other aspects of the law are similar for the chemical arts and biotechnology arts, but require a slightly different application. The issue of enablement falls into this category. The "make and use" components of enablement provide an analogous but not identical situation for chemicals and DNA. A claim for a chemical compound may not be enabled, because the specification does not teach a person of skill in the art to *make* the compound. Similarly, a claim for a DNA compound may not be enabled because the specification does not teach how to *use* the molecule.

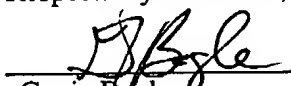
Grouping of Claims

The claims have been divided into two groups: Group I includes claims to the full-length sequences and claims reciting hybridization, and Group II includes claims to fragments. Claims to the fragments do not stand or fall with the claims for the full-length sequence and claims for hybridization, because the claims to fragments can be viewed as a species where the full-length sequence is the genus. A species is separately patentable from the genus because it is a novel invention. The claims for fragments involve different facts and different rejections than the claims involving full-length sequences and hybridization language. Even if Group I claims are found to be unpatentable, Group II claims could still be found patentable.

VII. CONCLUSION

Appellants submit that the pending claims 43-44 and 49-65 are patentable. It is respectfully requested that the Board reverse the final rejection of the subject matter of these claims for the reasons given above.

Respectfully submitted,



Gavin Bogle

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Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (617) 665-8079
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